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Impaired prenatal and postnatal growth in Dutch patients with phenylketonuria

P H Verkerk, F J van Spronsen, G P A Smit, R C A Sengers, on behalf of the National PKU Steering Committee

Abstract

Objective **– To assess whether physical growth is affected in early treated Dutch patients with phenylketonuria (PKU).**

Methods **– The birth weights of all 137 early detected patients with PKU born in the period from 1974 to 1988 in the Netherlands were compared with reference values. Height, head circumference, and weight were measured at the age at which treatment started (commonly about 2–3 weeks), at 6 months of age, and yearly from the child's first birthday up to the age of 10 years. These measurements were compared with reference values.**

Results **– The adjusted birth weight in patients with PKU was 141 g (95% confidence interval (CI) 66 to 216 g) less than Dutch reference values by Kloosterman and 103 g (95% CI 9 to 196 g) less compared with the birth weight of another reference group. At the age at which treatment started, z scores of patients for height by age were −0·23 (95% CI −0·44 to −0·02) and z scores for head circumference by age were −0·25 (95% CI −0·44 to −0·06). From the age at which treatment started up to the age of 3 years z scores for height by age further decreased to −0·74 (95% confidence interval −0·93 to −0·56), after which no additional decrease occurred. In contrast, z scores for head circumference increased from −0·25 at the first visit to 0·08 (95% CI −0·14 to 0·30) at the age of 1 year, after which they remained close to zero. Weight by height was close to the expected centiles for all ages.**

Conclusion **– Patients with PKU are growth retarded at birth and have smaller head circumferences than the normal population. In Dutch patients further growth retardation occurs in the first three years of life.**

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TNO Institute of Preventive Health Care, Leiden, The Netherlands
P H Verkerk

Department of Paediatrics, University Hospital of Groningen, The Netherlands
F J van Spronsen
G P A Smit

Department of Paediatrics, University Hospital of Nijmegen, The Netherlands
R C A Sengers

Correspondence to:
Dr P H Verkerk, TNO Institute of Preventive Health Care, Department of Social Paediatrics and Child Health, PO Box 124, 2300 AC Leiden, The Netherlands.

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Phenylketonuria (PKU) is a disorder in which the amino acid phenylalanine cannot be converted into tyrosine. The clinical manifestations of PKU include mental retardation as well as behavioural and dermatological problems.[1] Early experience with a low phenylalanine diet showed a positive effect on mental development,[2] but a negative effect on physical growth.[3 4] These findings have led to dietary improvements.[5] As a result of these improvements, detrimental effects on growth, if present, are likely to be less apparent nowadays. Only studies with a large number of patients have sufficient statistical power to detect these effects. To our knowledge the only longitudinal study that has provided information on the growth of a large number of patients with PKU is the American collaborative study of children treated for phenylketonuria. The results of this study have shown that in the period from birth to 10 years of age, children with PKU had almost identical height for age and head circumference for age (only followed up to 7 years of age), but were heavier than reference children.[6–8] A Swiss study also could not detect impairments in growth, but this study included only 20 patients with PKU.[9] In contrast, Dutch patients with PKU have been found to be smaller than would be expected from national standards.[10 11] As these analyses were cross sectional, it is unclear whether they reflect a smaller stature before the start of treatment, growth failure after treatment, or a combination of the two. We therefore performed a longitudinal analysis to answer this question.

Patients and methods

After a trial which started in 1968, nationwide screening for PKU in the Netherlands began on 1 September 1974. From the start of the screening all children with positive screening results were referred to eight university paediatric child clinics only. All parties taking part in the screening process or in the treatment of the patients, such as paediatricians, dietitians, biochemists, and psychologists, are members of the National PKU Steering Committee. The task of the committee is to monitor the screening process as well as the mental and physical development of the patients. The committee also sets up guidelines for diagnosis and treatment. To monitor the development of the patients, growth measurements and the results of developmental tests are registered at the Central PKU Registry. The committee considers a patient to have PKU if plasma phenylalanine concentrations are (a) $\geq$500 μmol/l in the untreated newborn infant and (b) if the tolerance for phenylalanine is $\leq$50 mg/kg/day at the age of 1 year.[11]

To follow the growth of each patient, height, head circumference, and weight were measured at the first diagnostic visit (usually before the age of 3 weeks), at the age of 6 months, and yearly as close as possible to the child's birthday. In this study we analysed the results of all measurements performed up to

the age of 10 years. At the first diagnostic visit, information on the child's birth weight and gestational age, height of the parents, parity of the mother, and country of origin of the mother were collected. Information on socioeconomic status (defined by type of health insurance, which is a proxy for family income) was collected in 1988. Height and head circumference were recorded in mm and weight in kg to two decimal places. The study population consisted of all 137 early detected and treated patients with PKU born during the period 1 September 1974 to 31 December 1988.[11]

We used four different reference groups, two in the analysis of birth weight and two in the analysis of follow up growth measurements. For the analysis of birth weight we used as reference values the Dutch growth standards of Kloosterman as well as results of the SMOCC study.[12 13] A limitation of the Dutch growth standards of Kloosterman is that they only allow correction of birth weight for gestational age, sex of the child, and parity of the mother. Birth weight was converted into z scores by subtracting the expected mean birth weight for that gestational age, sex, and parity, and dividing by its standard deviation. The SMOCC study is a representative, population based sample of 2151 (response 97%) live births during the period April 1988 to October 1989. In this study, information on the child's birth weight, gestational age, parity, and sex as well as other possible confounding factors such as the height of the parents, country of origin of the mother, and socioeconomic status (defined by type of health insurance) was collected at the age of about two to three weeks after birth. We used linear regression analysis to assess the unadjusted and adjusted difference in birth weight between patients with PKU and the SMOCC subjects.

Follow up growth measurements were compared with Dutch reference values[14] and the international reference values of Nellhaus.[15] The Dutch reference values are based on a representative sample of children born to parents of Dutch origin with a birth weight ≥2500 g. For this analysis the study group was therefore restricted, leaving 116 (85%) patients of Dutch origin with a birth weight ≥2500 g for analysis. The Dutch values only contain reference values on head circumference up to the age of 1 year. We therefore used as a second reference group the international values for head circumference provided by Nellhaus.[15]

As the measurements were not performed at exactly the same ages in all children, height and head circumference were converted into z scores by subtracting the expected mean measurement for that age in days and sex, and dividing by its standard deviation. As weight by height is not normally distributed,[14] we calculated the percentage of the patients that had a weight by height below the 10th centile and the percentage that had a weight by height above the 90th centile.

Results

BIRTH WEIGHT

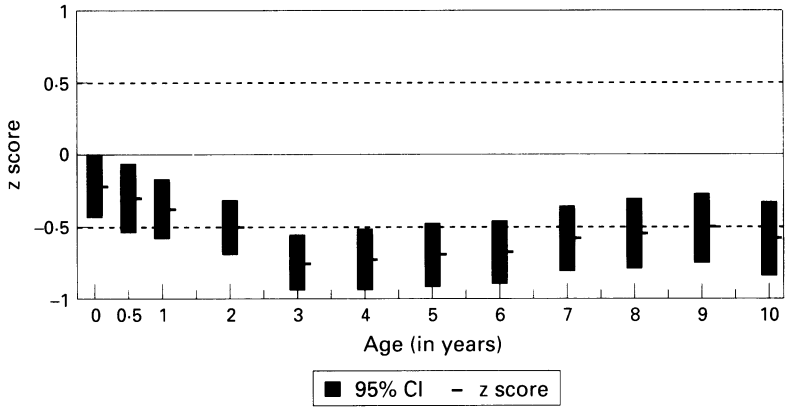
The mean birth weight of the 137 patients with PKU was 3271 g (SD 564 g). After adjustment for gestational age, sex, and parity, the patients weighed 141 g (95% confidence interval (CI) 66 to 216 g) less than expected from the Dutch growth standards of Kloosterman. The percentage of patients with a birth weight adjusted for gestational age, sex, and parity less than the 10th centile ('intrauterine growth retardation') was 19 and the mean z score was −0·36 (table 1). Unexpectedly, a linear trend seemed to exist between year of birth and mean score for birth weight. Patients born in the 1970s seemed to be lighter than patients born in the 1980s (correlation coefficient 0·20, p=0·02). Of the 137 patients 32 were siblings. In an analysis in which only the first affected child was chosen, so that families are counted only once, the average reduction in birth weight compared with the Dutch growth standards was 129 g (95% CI 51 to 207 g).

Before adjustment for confounding variables the mean birth weight of the PKU children was 129 g (95% CI 29 to 228 g) lower than the birth weight of the children in the SMOCC study. After adjustment for gestational age,

Table 1 Centiles and z scores for birth weight, and height by age and head circumference by age at diagnosis in the first three weeks of life of Dutch patients with PKU compared with Dutch reference values[12 14] and differences in birth weight compared with the SMOCC study.[13] Values are number (%) except where stated otherwise

	Dutch reference values							*SMOCC*
Birth cohort	*<2·3*	*2·3–9*	*10–90*	*91–97·7*	*>97·7*	*Total*	*Mean (SE) z score*	*Adjusted differences in g (SE)*
Birth weight								
1974–8	1 (3)	8 (23)	24 (69)	2 (6)	2 (7)	35 (100)	−0·61 (0·16)	−214 (81)
1979–83	3 (6)	7 (15)	32 (68)	3 (6)	1 (3)	47 (100)	−0·35 (0·19)	−109 (68)
1984–8	2 (4)	5 (9)	46 (87)	0	1 (2)	53 (100)	−0·20 (0·12)	−22 (69)
Total	6 (4)	20 (15)	102 (76)	5 (4)	4 (4)	135 (100)	−0·36 (0·09)	−103 (48)
Height by age*								
1974–8	1 (3)	4 (13)	21 (70)	2 (7)	2 (7)	30 (100)	−0·10 (0·21)	
1979–83	4 (11)	6 (16)	24 (63)	3 (8)	1 (3)	38 (100)	−0·41 (0·20)	
1984–8	1 (2)	5 (11)	34 (77)	3 (7)	1 (2)	44 (100)	−0·16 (0·16)	
Total	6 (5)	15 (13)	79 (71)	8 (7)	4 (4)	112 (100)	−0·23 (0·11)	
Head circumference by age*								
1974–8	4 (13)	3 (10)	23 (77)	0	0	30 (100)	−0·50 (0·20)	
1979–83	4 (11)	5 (14)	24 (67)	2 (6)	1 (3)	36 (100)	−0·44 (0·21)	
1984–8	4 (9)	6 (14)	31 (72)	2 (5)	0	43 (100)	−0·54 (0·18)	
Total	12 (11)	14 (13)	78 (72)	4 (4)	1 (1)	109 (100)	−0·50 (0·11)	

*Restricted to 116 patients for reasons of comparison with reference values (see methods).



Mean z scores of height by age of Dutch patients with PKU.

sex, parity, height of the parents, country of origin, and socioeconomic status the difference was 103 g (95% CI 9 to 196 g). The prevalence of preterm birth (<37 weeks) was 5·9% in the patients with PKU and 6·9% in the children of the SMOCC study (χ^2 0·07; df=1; p=0·79).

FOLLOW UP GROWTH MEASUREMENTS

Measurements available for analysis

By the time this study was performed all 116 patients of Dutch origin with a birth weight of 2500 g or higher had reached the age of at least 3 years. The number of patients that had reached the age of 4 was 107, whereas 58 patients were 10 years or older. The percentage of height by age and weight by height measurements available for analysis compared with the number of patients that had reached the age at which measurements should take place was 90% or higher for all ages, except at the age of 10 years (84%). Head circumference by age was available for 83% or more of patients in the first year of life. From the age of 2–10 this percentage varied from 52 to 72.

Table 2 Head circumference by age of Dutch patients with PKU compared with Dutch reference values[14] and international reference values of Nellhaus[15]

Age of measurement (years)	*Dutch values*	*Values of Nellhaus*
	Mean z score (95% CI)	*Mean z score (95% CI)*
0	−0·50 (−0·72 to −0·28)	−0·25 (−0·44 to −0·06)
0·5	−0·31 (−0·54 to −0·08)	−0·02 (−0·23 to 0·20)
1	−0·06 (−0·28 to 0·16)	0·08 (−0·14 to 0·30)
2	NA	0·07 (−0·20 to 0·34)
3	NA	0·06 (−0·21 to 0·33)
4	NA	0·09 (−0·21 to 0·38)
5	NA	0·07 (−0·31 to 0·45)
6	NA	0·27 (−0·08 to 0·61)
7	NA	0·09 (−0·28 to 0·47)
8	NA	0·17 (−0·18 to 0·52)
9	NA	0·19 (−0·11 to 0·48)
10	NA	0·07 (−0·21 to 0·36)

NA=reference values not available.

Table 3 Weight by height in centiles of Dutch patients with PKU compared with Dutch reference values. Values are number (%)

Age of measurement (years)	*<10*	*≥10 and <90*	*≥90*	*Total*	*χ^2 (df=2)**	*p Value*
0	7 (6)	99 (91)	3 (3)	109 (100)	8·72	0·01
0·5	8 (7)	96 (86)	7 (6)	111 (100)	2·96	0·23
1	3 (3)	99 (87)	12 (11)	114 (100)	6·89	0·03
2	12 (11)	91 (81)	10 (9)	113 (100)	0·20	0·90
3	8 (7)	90 (81)	13 (12)	111 (100)	1·21	0·55
4	13 (13)	73 (72)	16 (16)	102 (100)	4·97	0·08
5	11 (12)	73 (78)	9 (10)	93 (100)	0·35	0·84
6	8 (10)	65 (81)	7 (9)	80 (100)	0·14	0·93
7	10 (14)	58 (82)	3 (4)	71 (100)	3·58	0·17
8	6 (9)	53 (83)	5 (8)	64 (100)	0·39	0·82
9	8 (14)	46 (78)	5 (9)	59 (100)	0·92	0·63
10	4 (8)	40 (82)	5 (10)	49 (100)	0·18	0·91

*Compared with expected frequencies.

Height by age

In the first three weeks of life the mean z score was −0·23 (95% CI −0·44 to −0·02) (table 1 and figure). For boys with PKU this z score is equal to a decrease in average height of 5 mm compared with the expected values. From this age up until the age of 3 years the mean z score further decreased to −0·74 (95% CI −0·93 to −0·56). This z score is equal to a decrease of 30 mm in the average height of boys with PKU compared with the expected values for boys of 3 years of age. After the age of 3 years no further decrease in z scores occurred (figure).

Head circumference by age

In the first three weeks of life the mean z score was −0·50 (95% CI −0·72 to −0·28) when Dutch reference values[14] were used for comparison and −0·25 (95% CI −0·44 to −0·06) when the values of Nellhaus[15] were used for comparison (tables 1 and 2). After this age the mean z scores became close to zero and were no longer statistically significant.

Weight by height

Weight by height was close to the expected values at any age (table 3). Statistically significant differences were found in the first three weeks of life and at the age of 1 year. In the first three weeks of life we found fewer children with PKU with a weight by height lower than the 10th centile and fewer children with PKU with a weight by height higher than the 90th centile than expected. At the age of 1 year the percentage of children below the 10th centile was lower than expected.

Discussion

We found that Dutch patients with PKU are growth retarded at birth and have a lower mean head circumference in the first three weeks of life than the normal population. We subsequently found that in the first three years of life further growth retardation occurred, whereas head circumference increased to normal.

A decrease in birth weight in patients with PKU has also been reported by Saugstad.[16] He found that the mean birth weight in patients with PKU was 500 g less than that of healthy siblings. However, this finding could not be confirmed by two other studies in which patients with PKU were compared with their unaffected siblings.[17 18] One of these studies found that patients with PKU weighed 51 g less,[17] whereas the other found that patients weighed 40 g less.[18] These differences were not statistically significant. As the number of patients with PKU in these studies was small

(40 and 56), the failure to find a statistically significant result could be due to low statistical power. These findings, combined with our results, suggest that patients with PKU are indeed growth retarded at birth, but that the size of the effect is likely to be smaller than reported by Saugstad.[16]

We previously reported a higher prevalence of congenital heart disease in patients with PKU.[19] We speculated that the slightly increased phenylalanine concentrations in the mothers of the patients may be the cause of the increased prevalence of congenital heart disease. These mothers are likely to be heterozygotes. Heterozygotes have increased phenylalanine concentrations compared with normal mothers, especially after protein intake and during pregnancy.[20 21] In the offspring of mothers with extreme phenylalanine concentrations during pregnancy (as in maternal phenylketonuria) the prevalence of congenital heart disease, microcephaly, and low birth weight is much increased compared with the normal population.[22] We could speculate therefore, that the findings of this study further support our hypothesis; at least they should cast some doubt on a statement of Knox that 'there is almost universal agreement that the infant with phenylketonuria is not clinically abnormal at birth'.[23]

An explanation for the growth retardation that occurred in the period from birth to the age of 3 years may be that deficiencies of phenylalanine, tyrosine (an essential amino acid in children with PKU), or other essential nutrients occur due to a strict dietary regimen. Especially in the first years of life patients with PKU are likely to be treated with severe phenylalanine restriction, as in these years of life the brain is considered to be very vulnerable to increased phenylalanine concentrations. Furthermore, during this period of life children may be more susceptible to the effect of an insufficient intake of nutrients because of their rapid growth. As the results of growth studies carried out by the American collaborative study of children treated for phenylketonuria were reassuring in that they did not show growth retardation, too little attention may since have been given to this subject. Our results show that the American findings may not be applicable to other countries, perhaps because of differences in dietary treatment, and that insufficient growth in patients with PKU may still be an important issue.

An important advantage of our study is the fact that it is population based and that the number of missing values is small, except for head circumference from the age of 2–10 years. It is therefore unlikely that selection bias occurred. Unexpectedly, the differences we found in birth weight between patients with PKU and reference values seemed to be less for patients born in the 1980s compared with those born in the 1970s. One might argue that the reduction in birth weight we found could, therefore, be due to temporal changes in population birth weight. There are three reasons why we consider this explanation to be less likely. First, a recent Dutch study could not detect temporal changes in birth weight for infants born in the period 1972 to 1982 compared with the Dutch reference values and concluded that these values are still valid.[24] Second, we showed that birth weight was reduced in comparison with two reference groups from different time periods: one based on birth weights from 1931 to 1967 (Dutch reference values)[12] and one based on birth weights from 1988–9.[13] Third, differences in height and head circumference in the first three weeks of life did not show a trend with year of birth. The relationship between birth weight and year of birth is, therefore, possibly only a chance finding.

The measurements in our study were performed in eight different centres by a number of different people, and without centralised examination of the measuring instruments. This may increase the amount of random error and thereby decrease the precision of the results as well as the statistical power. As so many different people in many different settings performed the measurements, however, it is unlikely that there will be a systematic error (lack of validity) in the measurements.

We conclude that patients with PKU are growth retarded at birth and have smaller head circumferences than the normal population. In Dutch patients further growth retardation occurs in the first three years of life.

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Oral immunoglobulins for rotavirus gastroenteritis

Rotavirus infection causes some 900 000 deaths throughout the world each year and in the United States alone it is responsible for about one million cases of severe infantile diarrhoea and 150 deaths. Doctors in Italy have recently reported a prospective, placebo controlled, double blind trial of oral immunoglobulin in acute gastroenteritis (Alfredo Guarino and colleagues, Pediatrics 1994; 93: 12–6).

Ninety eight children aged between 2 and 36 months (mean 15 months) admitted to hospital in Naples were randomly assigned to receive either immunoglobulin (Sandoglobulin) 300 mg/kg body weight or 5% glucose by mouth. Three were excluded from the trial because they vomited back the fluid given. Of the remaining 95 children, 71 had rotavirus in their stools, 10 salmonella, and 14 no detected pathogens. In rotavirus gastroenteritis there was a highly significant reduction ($p<0.00001$) in both duration of diarrhoea (76 v 131 hours) and duration of excretion of virus (113 v 179 hours) in the immunoglobulin treated group. Length of hospital stay was reduced from six to four days ($p<0.01$). The immunoglobulin preparation used has specific neutralising activity against all four rotavirus strains tested. There was no significant benefit from immunoglobulin in salmonella enteritis or in those where no pathogens were found.

The only serious disadvantage of this treatment seems to be its cost (US$200 to treat a baby of 10 kg). Presumably this will restrict its use in those parts of the world where it might be most beneficial.

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